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The normal human appendix: a light and electron microscopic study

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INTRODUCTION

During the last few years there has been great interest in the structure and function of the lymphoid system generally, but little attention has been paid to the human appendix (Raviola, 1975).

The mammalian appendix can be considered from two points of view: one, as a possible 'central' lymphoid organ that, like other gut-associated lymphoid tissues, may be concerned with the maturation process of B lymphocytes (Perey, Cooper & Good, 1966; Fichtelius 1967), complement receptor B lymphocytes (Calkins Carboni & Waksman, 1975), or IgA precursor B lymphocytes (Craig & Cebra, 1975); and two, as an involuted structure with at most a 'circumstantial' lymphoid role. This second view is phylogenetically supported because the caecum has always been, both anatomically and functionally, digestive system-dependent: lymphoid infiltration may be simply a consequence of a recession in its primitive function (Patzelt, 1936).

In an attempt to determine if the human appendix has morpho-functional regions similar to the thymus-dependent and thymus-independent regions of other lymphoid organs (Parrot, de Sousa & East, 1966; Nopajaroonsri, Luk & Simon, 1971), a study has been made of the appendix in children.

MATERIALS AND METHODS

Human appendices removed at operation from 3 to 12 years old children were used. Most of the appendices were pathological in places. They were sectioned transversely for the determination of normal and diseased regions, the normal areas being chosen for light and electron microscopy. The criteria for normality were absence of ulceration, haemorrage distention by coprolites and/or obliteration of the lumen on macroscopic examination, and relative absence of neutrophilic granulocytes on microscopic examination.

Light microscopy

Samples were fixed in Bouin-Hollande, embedded in paraffin and sectioned at 6 μm. Sections were stained by a modified Dominici's method (Gorgollón & Krsulović, 1973), with an alcian blue–PAS–metanil yellow sequence, and by Gomori's method for reticulum and collagent (Gridley, 1960).

Electron microscopy

Selected portions of the samples were fixed in 6 % glutaraldehyde, pH 7·4, in 0·1 M-cacodylate buffer for two to three hours at 4 °C, rinsed in buffer, and cut into small cubes not more than 1 mm thick. Then they were post-fixed in OsO_4, stained '*en bloc*' with uranyl acetate, dehydrated in alcohol and acetone, and embedded in Epon.

Sections were cut with a Reichert UM-2 ultramicrotome: 1 μm sections were stained with toluidine blue and examined with the light microscope; 40 to 50 nm sections were stained with lead citrate and examined with a Zeiss EM-9 A electron microscope.

RESULTS

Three well defined regions, which will be described in detail with the electron microscopic observations, are present in children's appendices; they are: a sub-epithelial region or lymphoid lamina propria, a parafollicular region, and a follicular region of germinal centres.

Light microscopy

The epithelium that lines the crypts is similar to that of the mucous membrane of the large intestine; in this location intraepithelial lymphocytes are only occasionally found (Fig. 1). However, the epithelium of the luminal surface shows fewer goblet cells and a marked infiltration of lymphocytes and acidophilic leucocytes. This is particularly marked over the apices of germinal centres, where the epithelium tends to become cuboidal, and the boundary between it and the underlying lymphoid tissue sometimes disappears (Fig. 2). In such regions can be seen very faintly PAS-positive fine granulations in the cytoplasm of the epithelial cells. These granulations contrast with the alcian blue, or alcian blue–PAS–positive, goblet cell mucus. Sometimes strongly PAS–positive epithelial cells can also be found (Fig. 2)

In the lamina propria an almost typical lymphoid tissue, with many plasma cells, lymphocytes, acidophilic leucocytes, Russell bodies and mast cells was seen (Figs. 1, 2). Plasma cells, Russell bodies and any large macrophage inclusions are generally PAS-positive; mast cells have alcian blue-positive granulations. Lymphoid lamina propria merge into the underlying lymphoid tissue, which has a great number of lymphocytes and presents two different regions, one with germinal centres or true lymphoid follicles, with base, centre and apex generally well differentiated (Fig. 4), the other, or parafollicular region, with aggregations of mainly small lymphocytes. This region has a so-called 'primary follicle' character in areas where

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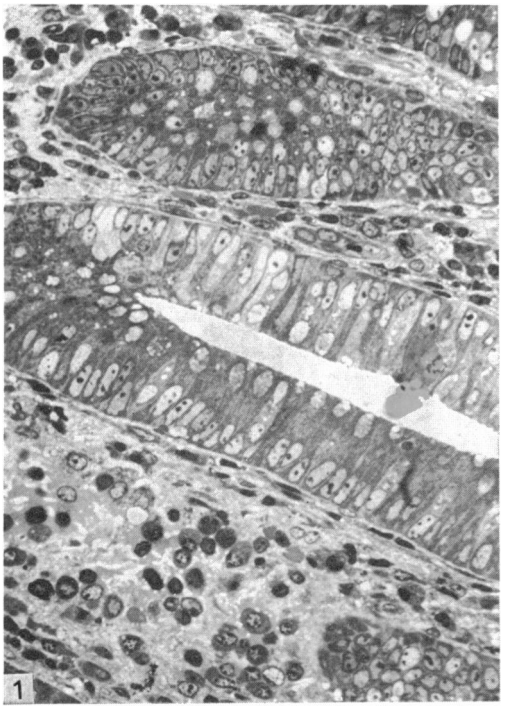
Fig. 1. Epithelium of crypt and sub-epithelial region Epon-embedded, toluidine blue-stained section. × 370.

Fig. 2. Outer epithelial surface. Note the intraepithelial lymphocytes (mainly at arrows) and the discontinuity in the basement membrane. In some areas the boundary between epithelium and lymphoid tissue disappears (upper arrow). Paraffin-embedded, alcian blue–PAS–haematoxylin–metanil yellow-stained section. × 380.

Fig. 3. Part of the parafollicular region near a marginal sinus. Note the relative absence of plasma cells and the motile appearance of some lymphocytes (arrows). Epon-embedded, toluidine blue-stained section. × 950.

Fig. 4. A well developed germinal centre showing base (A), centre (B) and upper periphery toward the free surface of the epithelium (C). Paraffin-embedded, eosin–orange G–toluidine blue-stained section. × 100.



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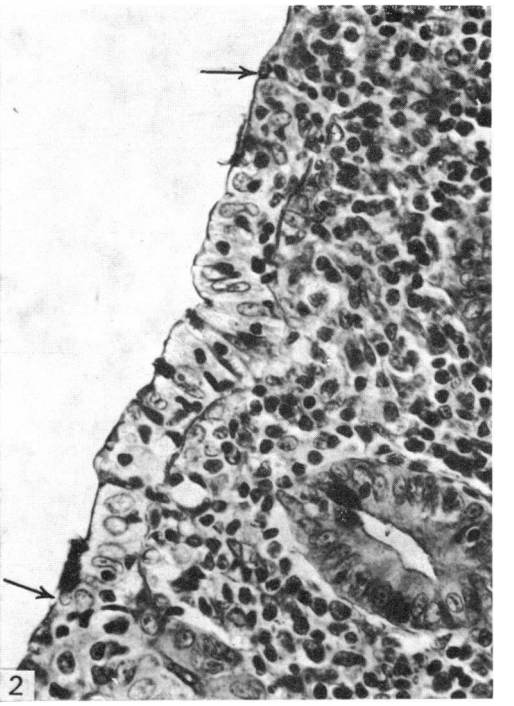

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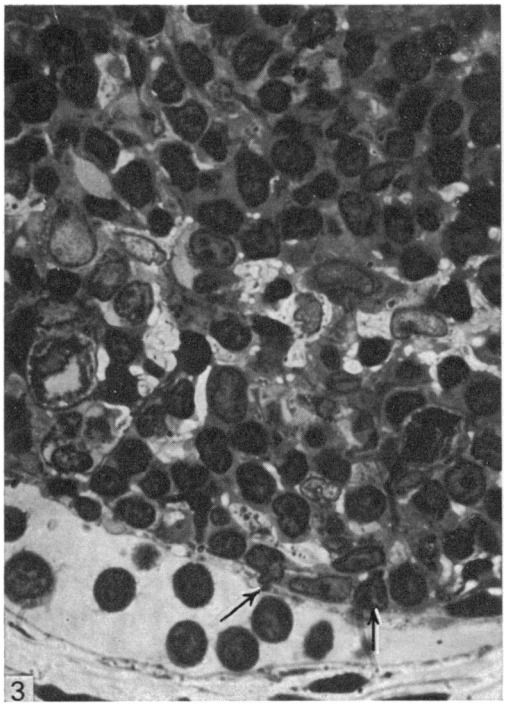

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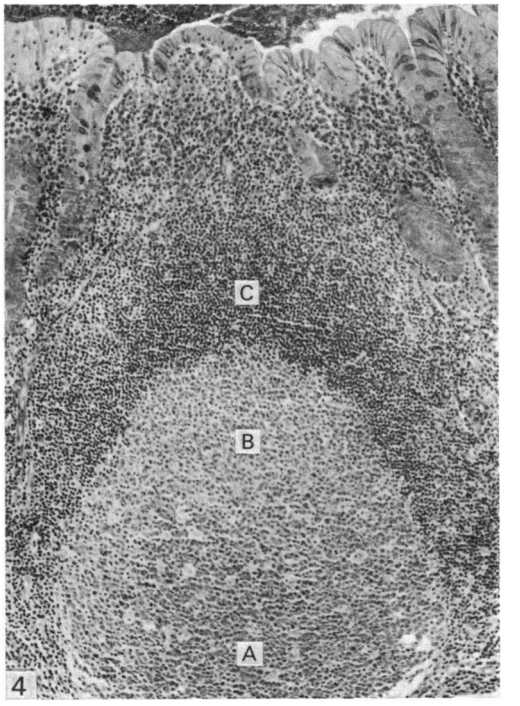

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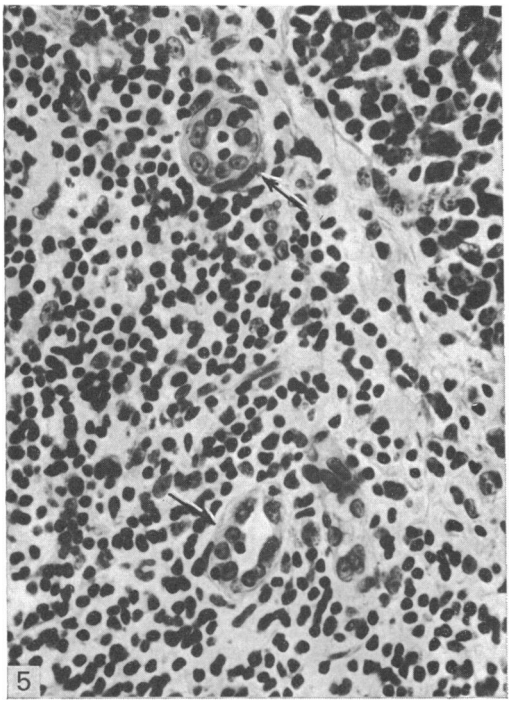
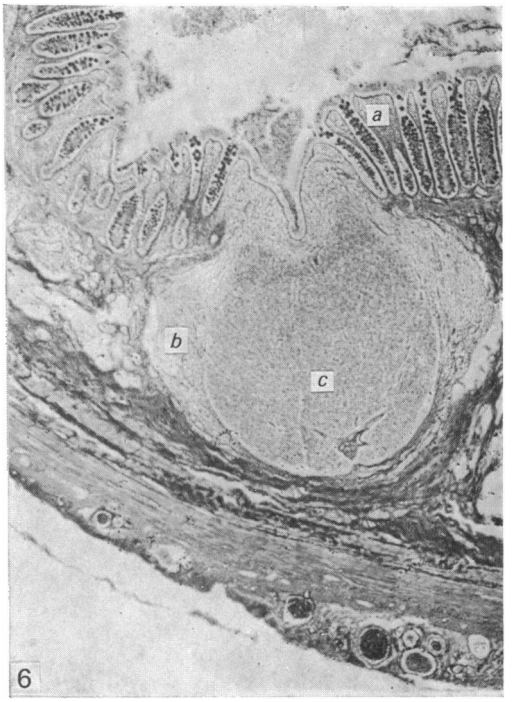




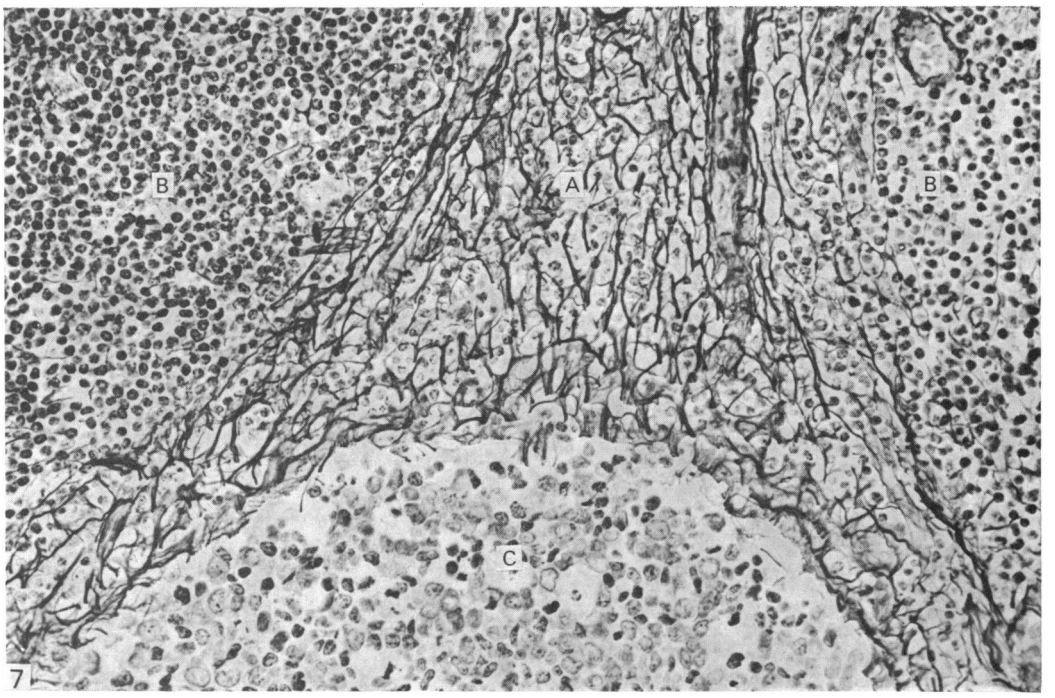


Fig. 5. Two post-capillary venules with tall endothelium in the parafollicular region (arrows). Paraffin-embedded, eosin–orange G–toluidine blue-stained section. × 350.

Fig. 6. General view of the three lymphoid regions of normal human appendix: (*a*) lymphoid lamina propria; (*b*) parafollicular region; (*c*) follicular region (germinal centre). Paraffin-embedded section, Gomori's reticulum stain. × 40.

Fig. 7. The three above-mentioned regions, easily distinguished by means of their fibrillar stroma. Paraffin-embedded section. Gomori's reticulum stain. × 300.

germinal centres are absent. The presence of high endothelial post-capillary venules, frequently with lymphocytes passing through their wall (Fig. 5), and the relative scarcity of plasma cells are other features of this region. A network of lymphatic vessels, which occasionally merges into a marginal sinus separates this area from the contiguous submucous connective tissue (Figs 3, 6).

The above-mentioned regions are easily distinguishable on the basis of their fibrillar stroma; this is coarse and broad in the sub-epithelial region, delicate in the parafollicular region, and practically absent in the germinal centres (Fig. 7).

Electron microscopy

Epithelium

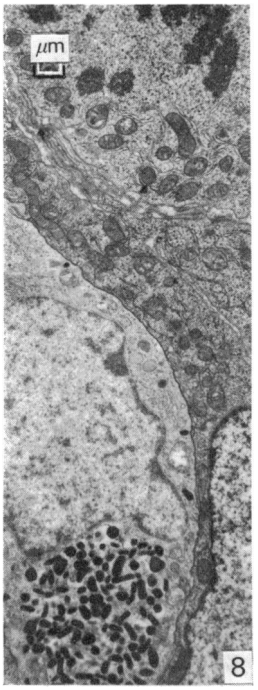
In the crypts the epithelium shows columnar cells, goblet cells and entero-endocrine cells; the latter belong to two types: one has small and irregularly shaped dense granulations 0·1 to 0·4 μm in diameter, similar to the argentaffin or entero-chromaffin cells found elsewhere in the digestive tract (Fig. 8); the other also has small granulations (about 0·1 to 0·2 μm), but they are rounded and of variable electron density (Fig. 9). The outer epithelial surface has columnar cells with short and irregularly arranged microvilli (Figs. 11, 12) and many mitochondria. Some of them show features of degenerating cells, such as dilated channels of rough endoplasmic reticulum, and a pycnotic nucleus, but there are no obvious changes in the numerous mitochondria until the final stages of cytoplasmatic disintegration.

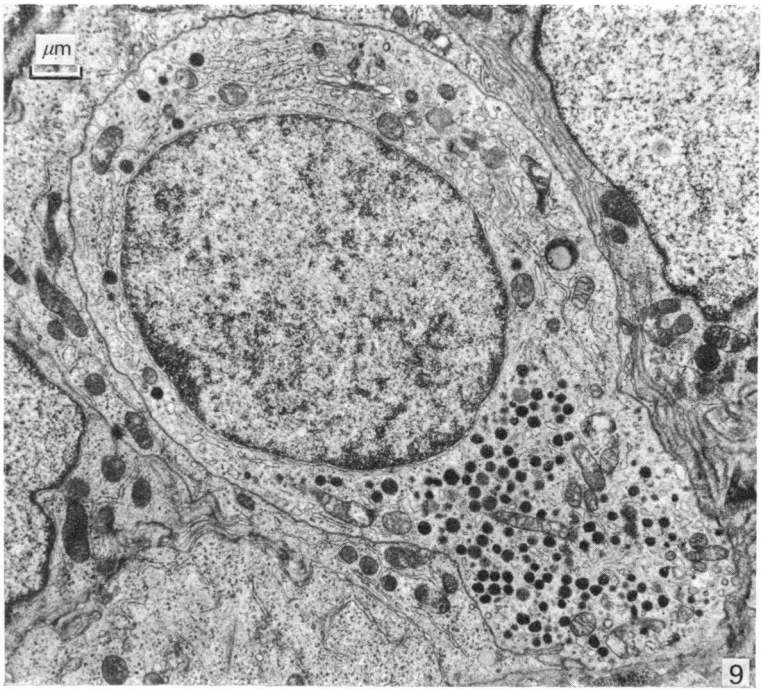
In these surface epithelial regions, intraepithelial lymphocytes are often observed. These cells are larger than the small lymphocytes of the lamina propria, and have a light cytoplasm with rather few organelles – some dense-matrix mitochondria, free ribosomes, a (usually) small Golgi apparatus, some small Golgi-derived vesicles and small dense granules (about 0·2 μm in diameter) similar to lysosomes (Figs. 10, 16). These 'light' lymphocytes can be found forming clusters or nests between epithelial columnar cells (Fig. 11–13), and they can be as big as blast cells. Examination of a number of these nests has shown that lymphocytes disrupt the basement membrane, between the epithelium and the underlying lymphoreticular tissue (Fig. 13). Lymphocytes were not actually seen passing through the apex of epithelial cells, although they were frequently in contact with the free surface of the epithelium. Acidophilic leucocytes, mast cells and intraepithelially degenerate leucocytes were occasionally found.

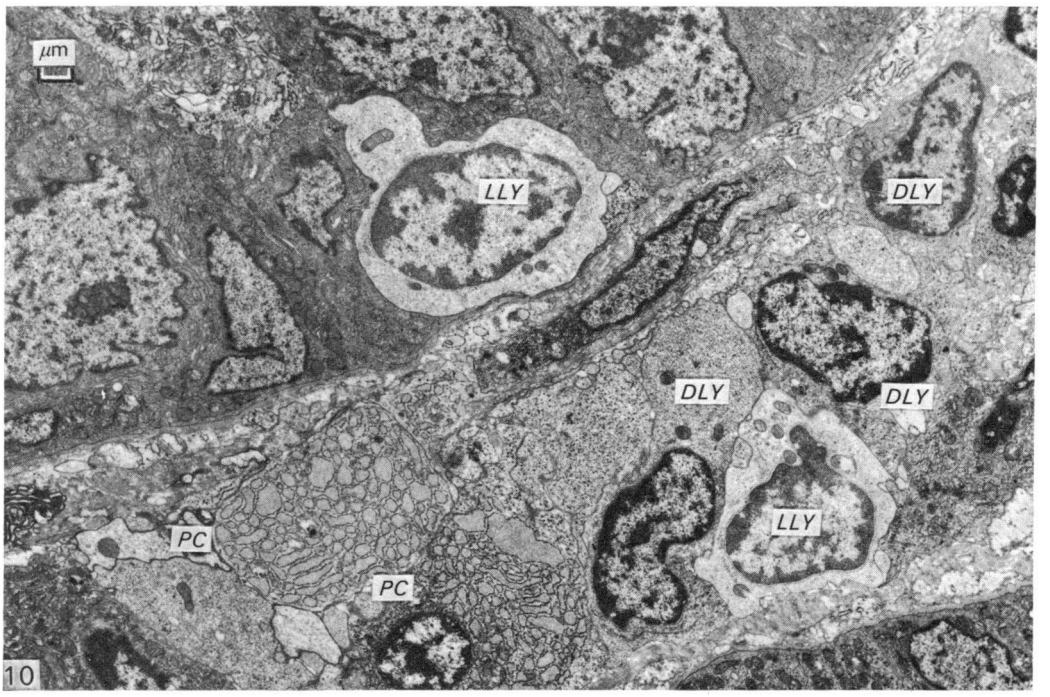
Sub-epithelial region (*lymphoid lamina propria*)

The most relevant feature of this region is the presence of many plasma cells. In addition, other free cells, including lymphocytes, acidophilic leucocytes and mast cells, are to be seen within a fibrocellular reticulum. This reticulum is composed of fibroblasts or fibre-associated reticular cells, undifferentiated reticular cells and reticular fibres. All reticular cells are irregular in shape, but some of them have cytoplasmic prolongations that intermingle with those of neighbouring reticular cells, and resemble dendritic cells. These last cells have a light cytoplasm with some cisternae of smooth and rough endoplasmic reticulum, several small vesicles and an irregular nucleus with fine chromatin. Sometimes they show granulations similar to lysosomes or residual bodies and a better developed endoplasmic reticulum (Fig. 15). Some typical macrophages can also be found. The fibre-associated reticular cells have a dense or dark cytoplasm, are provided with a clearly developed rough endoplasmic reticulum, and are in contact with bundles of collagen fibrils.

Lymphocytes are of 'light' and 'dark' types (described in the parafollicular region) and there are also intermediate forms (Figs. 10, 15). Occasionally seemingly





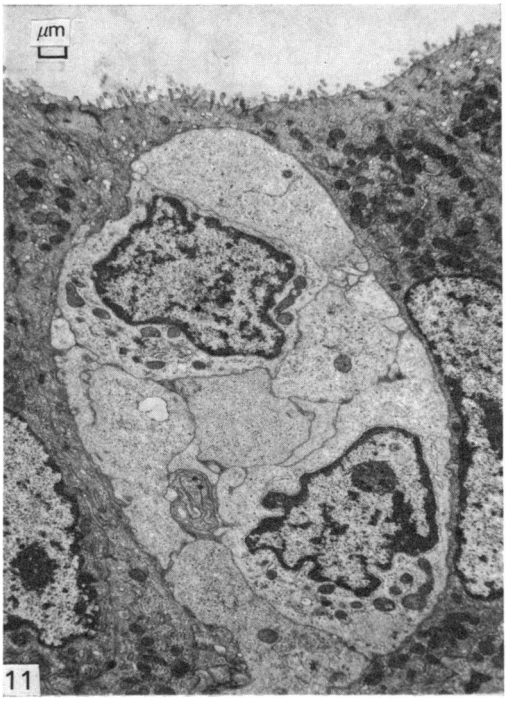


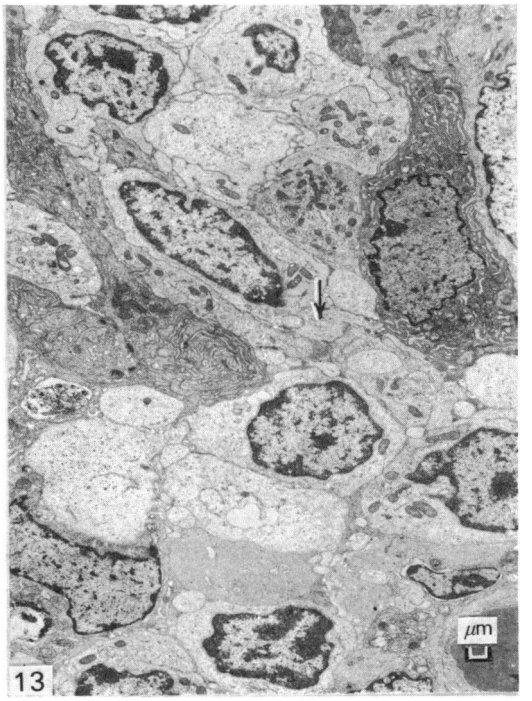
The following figures are electron micrographs of sections taken from material pre-treated in block with uranyl acetate, and stained with lead citrate.

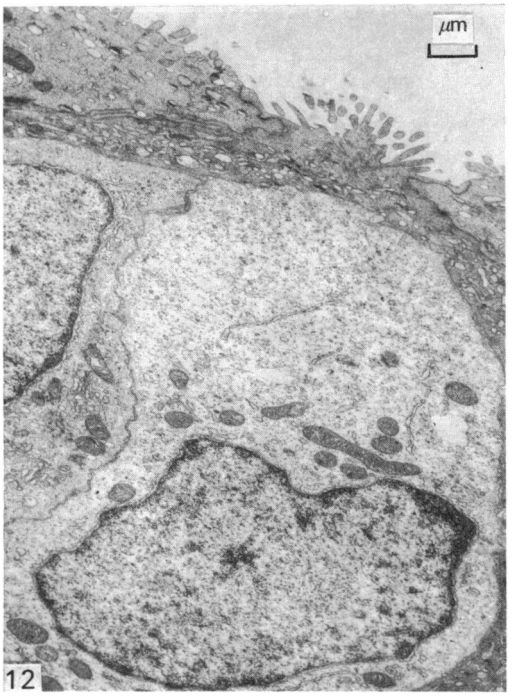
Fig. 8. An entero-endocrine cell with dense irregular granules. × 3600.

Fig. 9. An entero-endocrine cell with small round and variable electron-dense granules. × 6120

Fig. 10. Part of the epithelium of a crypt and the underlying lymphoid lamina propria. *LLY*, light lymphocytes (one of them intra-epithelial); *DLY*, dark lymphocytes; *PC*, plasma cells. × 4250.







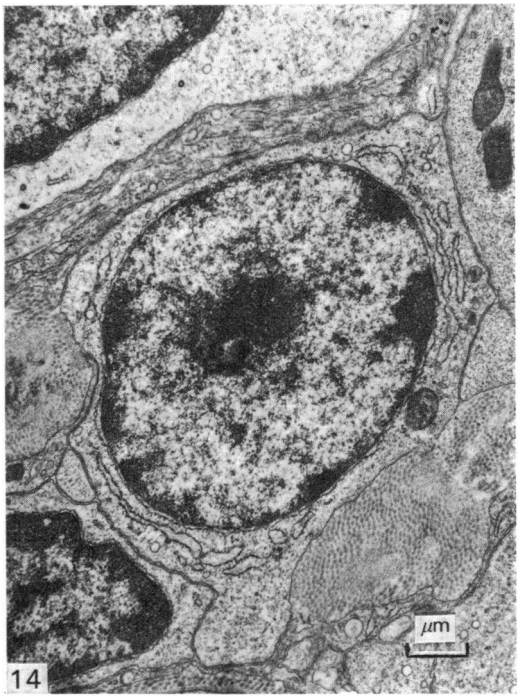
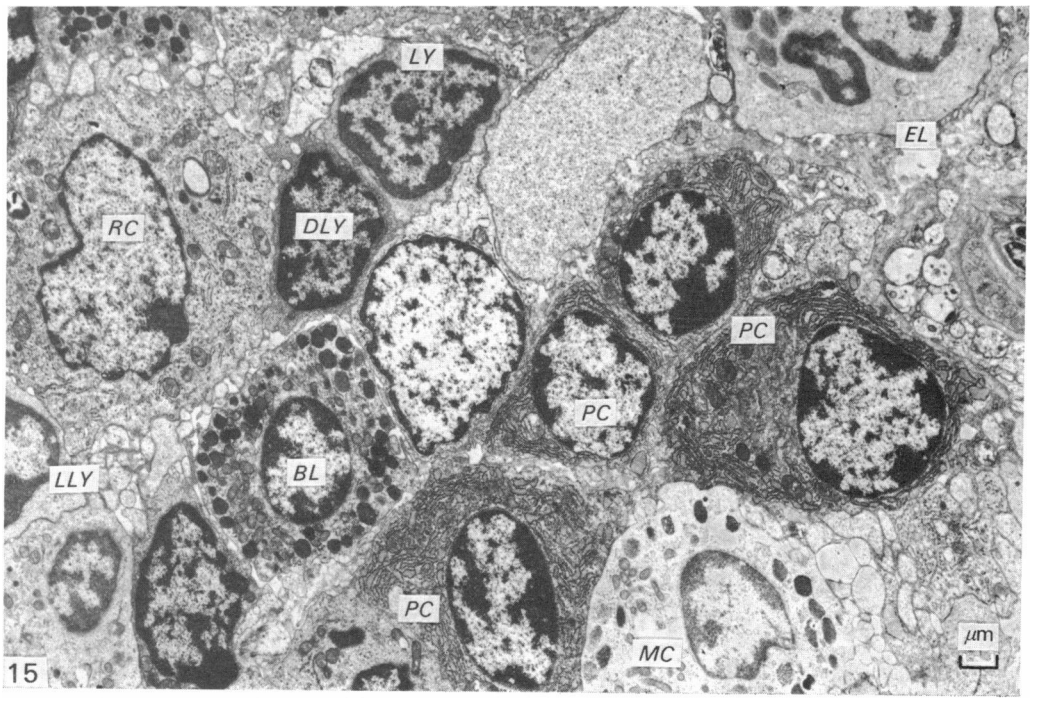


Fig. 11. An intra-epithelial nest of light lymphocytes. × 3520.

Fig. 12. Part of two blastoid lymphocytes in an intra-epithelial nest. × 6460.

Fig. 13. A cluster of lymphocytes that disrupts the basement membrane between epithelium and the underlying lymphoreticular tissue. × 3060.

Fig. 14. A blastoid lymphocyte near the epithelium, showing some features of a young plasma cell. Note that the cytoplasm is more like that of the light type of lymphocyte rather than the dark type (compare with Fig. 16). × 7900.



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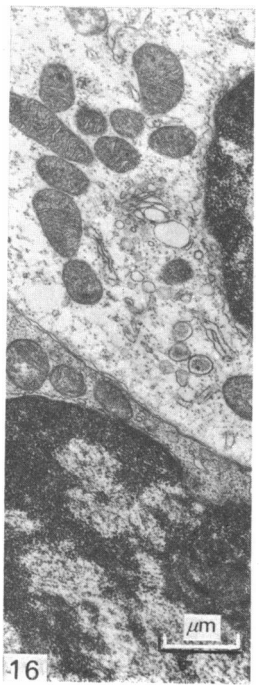

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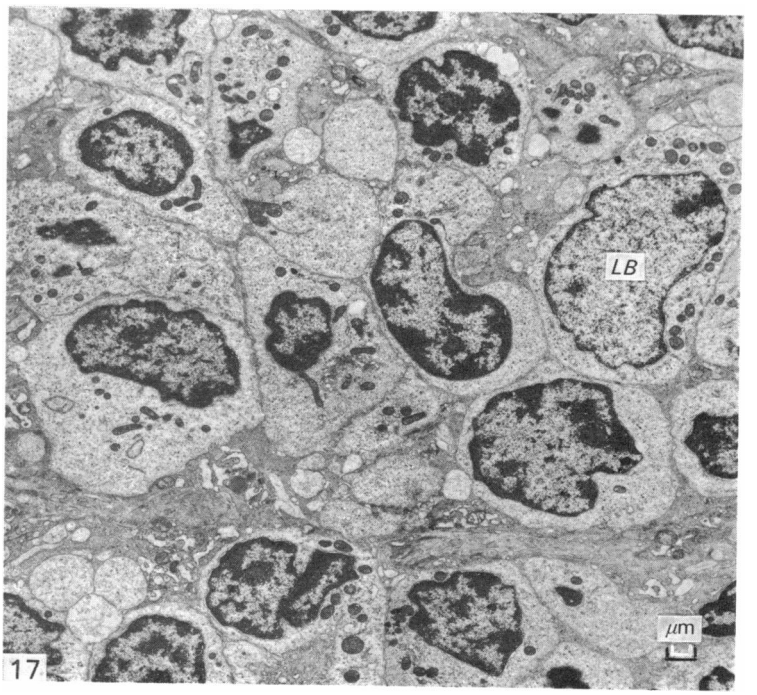

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intermediate stages between light lymphocytes and plasma cells can be found (Figs. 14, 18).

Plasma cells are seen in several maturation stages: their rough endoplasmic reticulum cisternae are often dilated by a more or less electron-dense secretion product and sometimes they are seen releasing this secretion, apparently by cellular lysis (Fig. 10).

In some places the reticular cell interdigitations and the density of the lymphocytes make this zone similar to the parafollicular region with which it merges. This is the case with the sub-epithelial layer that covers the apex of a true follicle (Figs. 13, 18).

Parafollicular region

The region is characterized by the density of lymphoid cells, amongst which small and medium size lymphocytes predominate. Plasma cells are scarce, and generally they are seen only at the boundary between this zone and the sub-epithelial region.

Like those of the sub-epithelial region, the small lymphocytes are of two types: light and dark. Light ones are characterized by cytoplasm which is paler and rather more abundant than in the dark lymphocytes, but with few organelles: the electron lucidity of the cytoplasm is due to the small number of ribosomes A Golgi complex and some isolated cisternae of smooth endoplasmic reticulum are also observed: mitochondria are commonly small and with dense matrix. However, the most relevant features of these lymphocytes are some small granulations about 0·2 μm in diameter, and some (probably) Golgi-derived vesicles (Fig. 16). Medium sized lymphocytes belong mainly to this variety: these cells have more abundant cytoplasm, and they become irregular in shape as they adapt themselves to the interstices of the tissue. Because of this they are barely distinguishable from some reticular cells (Fig. 17). Organelles are similar to those of the small light lymphocytes except that there are more mitochondria, a better developed Golgi complex, some multivesicular bodies and some cisternae of rough endoplasmic reticulum. Although there is no marked increase in free ribosomes, some medium-sized lymphocytes of this type show better developed rough endoplasmic reticulum and prominent nucleoli (Figs. 14, 18).

Dark lymphocytes are scarcer and in general they correspond to the prototype already described. Their characteristic feature is exiguous cytoplasm, although there are many free ribosomes (Fig. 16). Medium-sized lymphocytes of this last type are very uncommon. Intermediate forms between light and dark lymphocytes are numerous, and sometimes in the majority.

Two types of reticular cells are seen. One type has dense cytoplasm and is similar to the fibre-associated reticular cells of the lymphoid lamina propria. Like these cells, they have a dense chromatin nucleus, fine cytoplasmatic filaments and some

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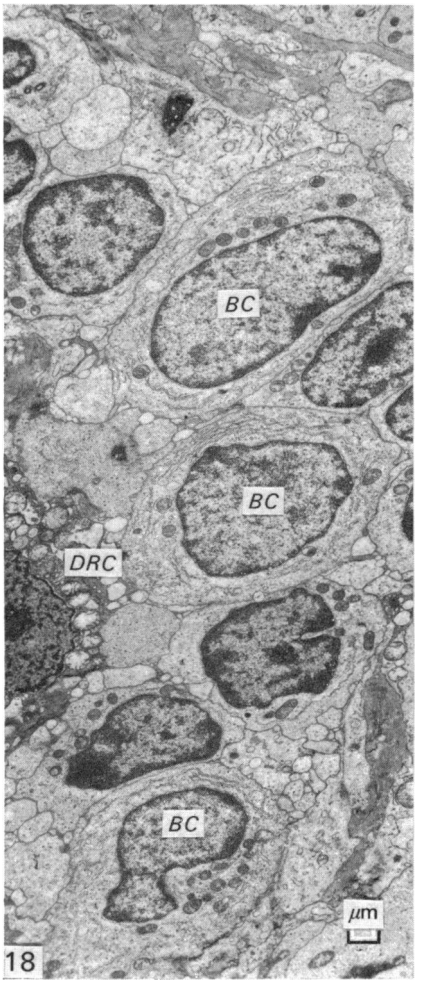
Fig. 15. Sub-epithelial region (lymphoid lamina propria,) showing some of the cells commonly present. *LLY*, light lymphocyte; *DLY*, dark lymphocyte; *LY*, dark–intermediate lymphocyte; *PC*, plasma cells; *RC*, light type reticular cell; *EL*, eosinophil leucocyte; *MC*, mast cell; *BL*, mast cell with some features of a basophil leucocyte. × 4680.

Fig. 16. Part of two well-differentiated types of lymphocyte: light (upper) and dark (below). Note the characteristic lysosome-like granules near the Golgi region of the light lymphocyte. × 10500.

Fig. 17. Part of the parafollicular region, showing several light lymphocytes and a blast cell of the same variety (*LB*). Some prolongations of dark fibre-associated reticular cells are also seen. × 3150.



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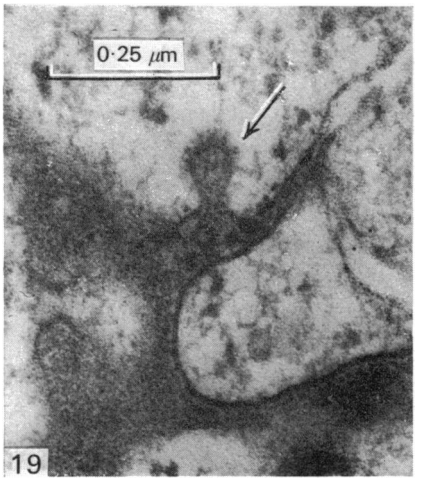

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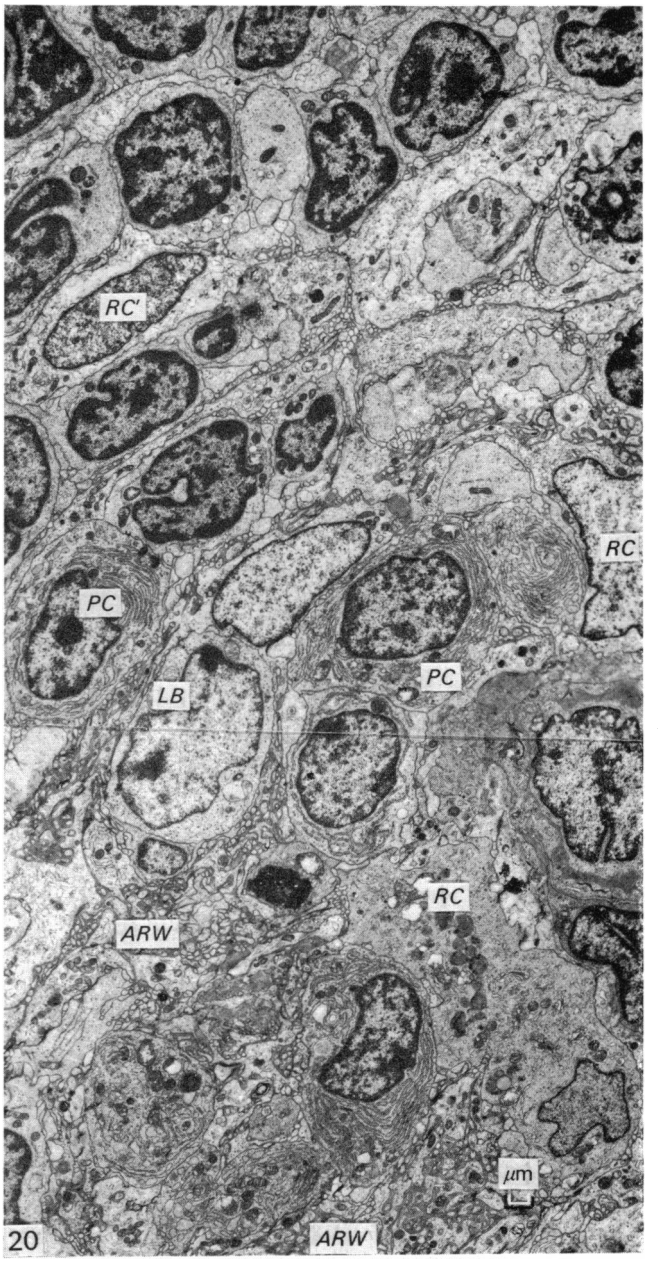

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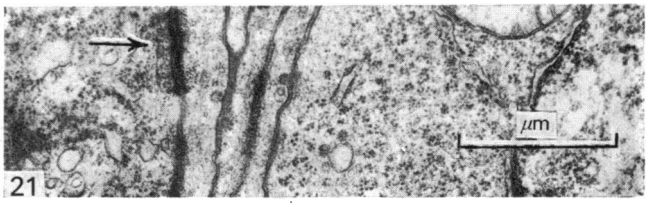

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cisternae of rough endoplasmic reticulum. The other type is similar to the irregular reticular cells of the lymphoid lamina propria, and frequently exhibits the features of dendritic reticular cells, with a great number of interdigitating prolongations. This type of cell sometimes has dense cytoplasm like that of fibre-associated reticular cells (Figs. 17, 18). Some reticular cells appear to be degenerating.

The post-capillary venules have tall endothelial cells with a well developed Golgi complex, Golgi derived microvesicles, dense matrix mitochondria, multivesicular bodies, some lysosomes and many cytoplasmic filaments (Fig. 22, inset). Lymphocytes, mainly of the light type, are seen migrating through the tall endothelium. The intercellular spaces can be broad and contain a fine granular or filamentous matrix; this material is found also over the surface of endothelial cells (Fig. 22). Occasionally, erythrocytes can be seen trapped between endothelial cells.

Lymphoid follicles (germinal centres)

The main features of germinal centres are the presence of large polyribosomal blast cells, some in mitosis, and dendritic reticular cells. Germinal centres are delimited basally by dense fibre-associated reticular cells and limiting reticular cells that resemble polyribosomal blast cells: near these cells there are large blast cells provided with many free ribosomes and polyribosomes, large light-matrix mitochondria, often swollen, and a few cisternae of rough endoplasmic reticulum (Fig. 21). Some of these blast cells, mostly the basal ones, seem to be reticular cells because of their irregularity, and the scarcity of free ribosomes. Between them can be found prolongations of blast cells and of dendritic reticular cells which, unlike dendritic-like cells outside the follicle, sometimes display desmosomes and cytoplasmic microtubules. The proportion of dendritic reticular cells increases towards the centre of the follicle. Here, the interdigitating cell spaces are broader and filled with a moderate electron-dense substance. Coated vesicles opening to these spaces, and apparently engaged in micropinocytosis, are frequently observed (Fig. 19).

Dense reticular cells, light and dark lymphocytes, macrophages and plasma cells, are also found. Plasma cells are abundant in the central region of the follicle (Fig. 20).

DISCUSSION

It is well known that lymphocytes are frequently intraepithelial (Meader & Landers, 1967; Toner & Ferguson, 1971; Loo & Chin, 1974). However, one difference between the surface epithelium of the appendix and that of other regions of the digestive and respiratory tracts is the presence of nests of lymphocytes or immunoblasts inside or between epithelial cells. Such nests or clusters of lymphocytes have

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Fig. 18. Part of the sub-epithelial region, apparently over the apex of a germinal centre, that shows some features of the parafollicular region. Note the blast cells with rough endoplasmic reticulum (*BC*), and part of a degenerating dark reticular cell (*DRC*). × 3660.

Fig. 19. A coated vesicle opening to the intercellular spaces of the 'antigen-retaining' web in the central region of a germinal centre. × 90230.

Fig. 20. Partial view of the upper part of a germinal centre, with its crescentic cap of small lymphocytes (upper left). Note the antigen-retaining web in the central region of the follicle (*ARW*), and the transition of dendritic reticular cells to other light reticular cells at the periphery (*RC-RC'*). PC, plasma cells; *LB*, light blastoid cell. × 3060.

Fig. 21. Part of a polyribosomal blast cell (to the right) in the base of a germinal centre. The arrow shows a desmosome-like attachment. × 21000.

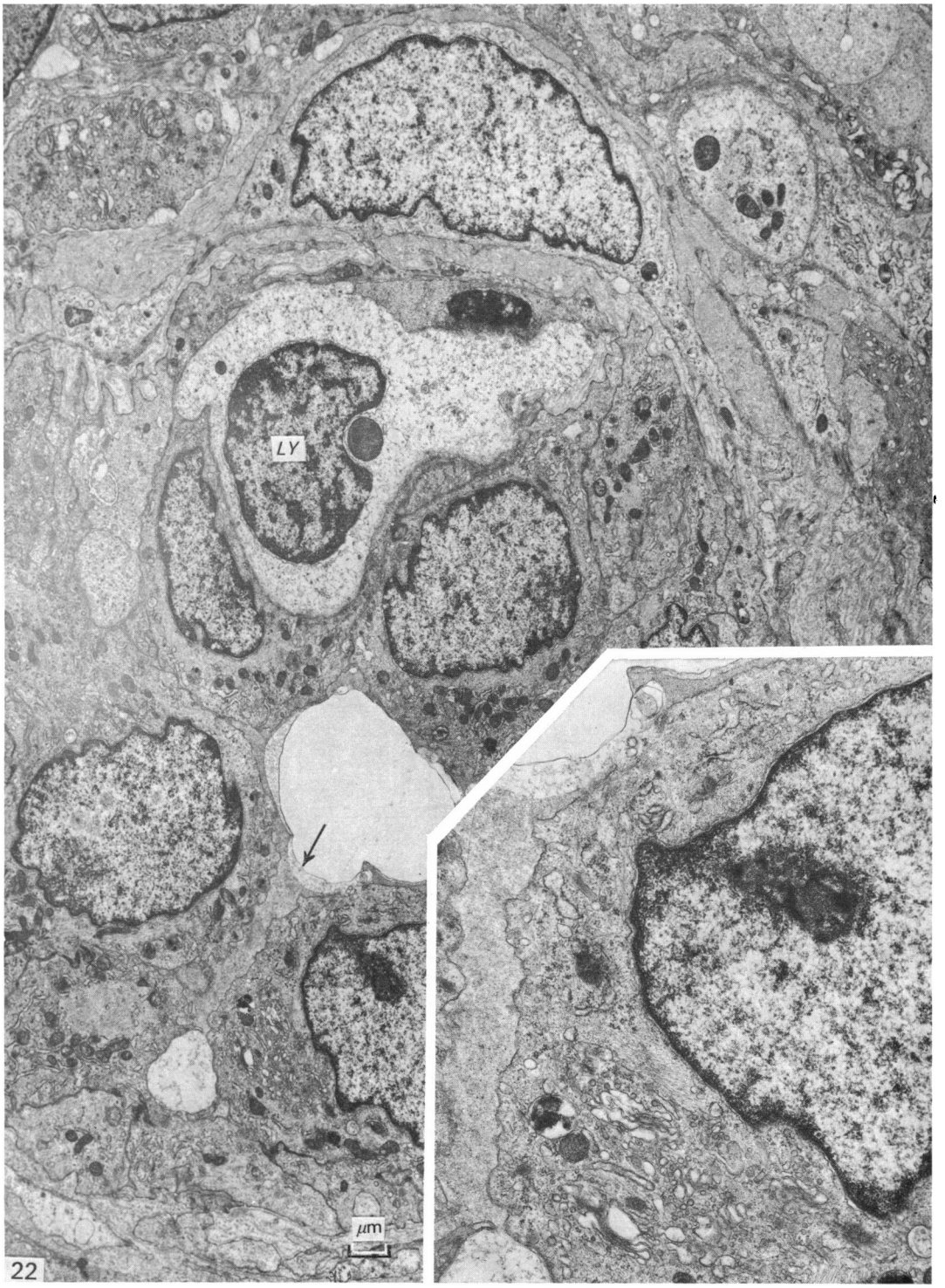

Fig. 22. A post-capillary venule with tall endothelium, and with a light lymphocyte (*LY*) passing through its wall. Arrow indicates the surface coat material in a region where it separates two adjacent endothelial cells. The inset shows some fine structural features of one of these endothelial cells. × 5530; inset × 14000.

been described in the rabbit appendix (Shimizu & Andrew, 1967; Nieuwenhuis, 1971). We are able to observe that these nests disrupt the basal membrane. On the supposition that lymphocyte clusters are formed gradually by a sequential migration of lymphocytes into the epithelium (Nieuwenhuis, 1971), this massive disruption of the basal membrane may be an indication of a return of these cells to the sub-epithelial lymphoid tissue after a period of intraepithelial maturation (Fichtelius, 1968). However, since these nests of blastoid lymphocytes belong mainly to the light type (see later), and transitional forms between them and plasma cells in the sub-epithelial region can be seen, it is possible that they undergo an intra-epithelial process of maturation or differentiation to become plasma cells.

Post-capillary venules with tall endothelium have been observed in lymph nodes, and in Peyer's patches, in the mouse (Chin & Hudson, 1971), and also in human palatine tonsils (Sordat, Hess & Cottier, 1971). Present electron microscopic findings are that the fine structure of these vessels is similar to that described in other lymphoid organs (Claesson, Jorgensen & Ropke, 1971), but it is interesting to note that these venules present a surface coat similar to that found over the epithelium of the large intestine (Schofield & Atkins, 1970), and it is significant that this material is also found between endothelial cells where they are sometimes separated. This material may correspond to the immunoglobulin surface coat found in these vessels (by immunofluorescence) and be one of the factors controlling lymphocyte recirculation (Sordat *et al.* 1971). It is suggestive that dark lymphocytes are very scarce, but light lymphocytes are numerous, within these venules.

'Light' and 'dark' lymphocytes have been frequently noted (Milanesi, 1965; Huhn, 1970; Gorgollón & Krsulović, 1973; Pereira, 1974), but their possible relation with T and B lymphocytes is not known, nor indeed whether the differences are fixation artifacts. The frequent presence of light lymphocytes within post-capillary venules, generally accepted as a pathway for re-circulating T lymphocytes (Raff, 1973; Cooper & Lawton, 1974), their abundance in appendix parafollicular regions, the supposition that intraepithelial lymphocytes are of T nature (Guy-Grand, Griscelli & Vassalli, 1975), and some resemblances between them and phytohaemagglutinin (PHA)-activated lymphocytes (Inman & Cooper, 1963), all support the view that these lymphocytes belong to the thymus-dependent T type.

However, in spite of certain PHA-stimulated lymphocyte resemblances, light lymphocytes in general have fewer ribosomes, while some show a relatively well developed rough endoplasmic reticulum similarly to cells stimulated with specific humoral response mitogens (Douglas & Fudenberg, 1969). Moreover, the fact that light lymphocytes are seen in the peripheral lymphoid organs, but not in the thymus (Pereira, 1974); the finding that human *B* lymphocytes seem to be larger than T lymphocytes (Polliack *et al.* 1973); and also (as found in the present study) that there seem to be transitional forms between light lymphocytes and plasma cells; all support the view that light cells are B lymphocytes. A possible resolution of this dilemma is to suppose that light lymphocytes, as well as the larger or villous lymphocytes observed under the scanning electron microscope (Baur, Thurman & Goldstein, 1975), are activated or mature forms of *both* T and *B* cells.

Owing to the presence of many plasma cells, the sub-epithelial region, and to some extent the germinal centres, must be bursa-dependent (thymus-independent) regions; while the parafollicular region, with its venules lined with tall endothelium, absence of plasma cells, and sparse fibrillar stroma, may be a thymus-dependent region (Nopajaroonsri, 1971). However, it is doubtful whether such zonal differentiation is

always as schematic as is generally assumed, because the appendix parafollicular region has some resemblance to the follicular region, and could be simply at an earlier stage of development.

In this respect, cells very like the dendritic reticular cells characteristic of germinal centres (Nossal *et al.* 1968; Hanna & Hunter, 1971), and the fibre-associated dark reticular cells (Weiss & Chen, 1974), are both found in the sub-epithelial and parafollicular regions. The former have no desmosomes and do not possess such ramified prolongations as the corresponding cell found in germinal centres, but they are similar in other fine structural characteristics. Very similar cells have been recently described in the human thymus (Kaiserling Stein & Müller-Hermelink, 1974), in the inner medullary region of the dog's thymus (Gorgollón & Ottone-Anaya, 1978) and in the peripheral lymphoid organs of mice (Steinman & Cohn, 1974): Thus they seem to be a type of cell present in lymphoid tissues generally. Further investigations are needed to explain their role in the immunological process.

SUMMARY

Human appendices from 3 to 12 years old children were studied by light and electron microscopy.

Three morphological zones were determined: sub-epithelial (or lymphoid lamina propria), parafollicular, and follicular. The fine structure of these regions has been studied and discussed with regard to the thymus-dependent and thymus-independent regions of other lymphoid organs. Two types of lymphocytes, 'light' and 'dark', and intermediate forms, were also found. The light ones are the more abundant in the epithelium and within the parafollicular post-capillary venules; they form groups or clusters between epithelial cells, becoming like blast cells and possibly maturing into plasma cells in the sub-epithelial region. Whether light lymphocytes are T or B or both is discussed.

The general conclusion is that the human appendix, at least in children, has the characteristics of a well-developed lymphoid organ, suggesting that it has important immunological functions.

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